UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/699,023	10/27/2000	Gang Chen	UTSB:675US/SLH	5751

7590 04/18/2002

Robert E. Hanson
Fulbright & Jaworski L.L.P.
Suite 2400
600 Congress Avenue
Austin, TX 78701

EXAMINER	
FORD, VANESSA L	
ART UNIT	PAPER NUMBER
1645	10

DATE MAILED: 04/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/699,023	Applicant(s) CHEN ET AL.	
	Examiner Vanessa L. Ford	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-74* is/are pending in the application.

4a) Of the above claim(s) *33-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-74* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Copy of page 31* .

DETAILED ACTION

1. Applicant's election without traverse of Group I, claims 1-32 is acknowledged. Claims 33-74 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Specification

2. In reviewing the specification, it appears that page 31 has been torn and a part of the narrative is missing. It is requested that a copy of page 31 be submitted with the response to this Office Action.

3. The specification is objected to be cause of the following informalities: The specification recites "Escherichia coli" (page 13), which is the genus and species of a microorganism and should be italicized. Correction is required is required.

4. The specification is objected because of the use of worldwide web addresses on pages 52 and 62. The worldwide web address can be readily changed and therefore, may not be available to the public. The specification should be reviewed for worldwide web addresses and the web address must be deleted from the specification.

Claim Objections

5. Claim 30 is objected to because it recites "FACS", which should be changed to "fluorescence activated cell sorting" at the first occurrence in the claims. Correction is required.

Drawings

6. The drawings are objected to by the Draftsman under 37 CFR 1.84 or 1.152. See the attached form PTO 948.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1,2, 4, 7, 13 and 22 recite the term "capable of". It is unclear as to what the applicant is referring? Thus, the metes and bounds of "capable of" cannot be ascertained. Clarification as to the meaning of this term is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-32 are rejected under 35 U.S.C. 102(b) as anticipated by Iverson et al (*WO 98/49286, published November 5, 1998).*

Claims 1-32 are drawn to a method of obtaining a bacterium comprising a nucleic acid sequence encoding a binding protein capable of binding a target ligand comprising

the steps of: providing a gram-negative bacterium comprising a nucleic acid sequence encoding a candidate binding protein, wherein said binding protein is expressed in soluble form in said bacterium; contacting said bacterium with a labeled ligand capable of diffusing into said bacterium; and selecting said bacterium based on the presence of said labeled ligand within the bacterium, wherein said ligand and said candidate binding protein are bound in said bacterium.

Iverson teach the screening of antibody libraries displayed on the cell surface. Iverson et al teach a method comprising: contacting the cells with a known amount of antibody and placing them in a solution of a known concentration of the analyte-conjugate along with an unknown concentration of the analyte (the test solution). Iverson et al teach that the analyte-conjugate competes with free analyte in solution for binding to the antibody molecules on the cell surface and that the mixture is centrifuged to pellet the cells and the fluorescence of the supernatant is measured. Iverson et al teach that fluorescence determinations may be made with a basic fluorimeter. Iverson et al teach that the "expression construct" is a genetic construct containing a nucleic acid coding for a gene product in which part or all of the nucleic acid is capable of being transcribed. Iverson et al teach the amplification of gene fragments (pages 39-43). Iverson et al teach that the host cell is a gram-negative bacterium, *E. coli* (claims 2-3, page 123) and that a plurality of DNA segments are incorporated into expression vectors and the vectors express antibodies or antibody fragments on the outer membrane surface (the periplasm) of *E. c*oli (claim 11, page 124). Iverson et al teach that a targeting sequence has been developed that when it is fused to normally soluble

proteins, it can direct soluble proteins to the cell surface (page 22). Iverson et al also teach that the polypeptide is elected from the groups consisting of an antibody or antibody fragment, an enzyme, a cytokine, a transcription factor, a clotting factor, a chelating agent, a hormone and a receptor (claim 4, page 123). Iverson et al teach that the cells displaying antibodies having affinity for a desired analyte are isolated and that identifying the antibody or antibody fragment expressing cells may be accomplished by methods of detecting the presence of the bound detectable label. Iverson et al teach that the labeled ligand can comprise radioactive, fluorescent, chemiluminescent, electrochemiluminescent, biological or enzymatic tags (page 51). Iverson teach that one aspect of this method is fluorescence activated cell sorting (FACS) and that high affinity clones, the production of soluble antibodies can be achieved easily without the need for further subcloning steps. Iverson et al teach that the clones may be maintained under standard culture conditions (about 24°C) (page 61) and employed to produce the selected antibody and production of antibody is limited only to the scaleup of the cultures (page 48). Iverson et al teach that the cells with the antibody displayed on the surface may themselves be attached to a solid support such as a membrane, dipstick or magnetic beads to further facilitate removal of the cells following the assay (pages 49 and 55). Iverson et al teach that cells were harvested and resuspended in PBS pH 7.4 at a concentration of 10^{10} cell/ml based on the $O.D._{600}$ to form a cell shock and some cells were resuspended in 15 % glycerol /water and stored at 70°C (i.e. hyperosmotic conditions and physical stress) (page 67). Limitations such as the ligand comprise a molecular weight of less than about 20,000 Da, less than about 5,000 Da

and a molecular weight greater than 600 Da and less than about 30,000 Da would be inherent in the teachings of the prior art.

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

9. Claims 1-32 are rejected under 35 U.S.C. 102(b) as anticipated by Georgiou *(U.S. Patent No. 5,866, 344, published February 2, 1999).*

Claims 1-32 are drawn a method of obtaining a bacterium comprising a nucleic acid sequence encoding a binding protein capable of binding a target ligand comprising the steps of: providing a gram-negative bacterium comprising a nucleic acid sequence encoding a candidate binding protein, wherein said binding protein is expressed in soluble form in said bacterium; contacting said bacterium with a labeled ligand capable of diffusing into said bacterium; and selecting said bacterium based on the presence of said labeled ligand within the bacterium, wherein said ligand and said candidate binding protein are bound in said bacterium.

Georgiou teaches a method of obtaining a bacterium comprising a nucleic acid sequence encoding a binding protein capable of binding a target ligand comprising the steps of: Obtaining antibodies from an expression vector library that may be prepared

from DNAs encoding antibodies or antibody fragments, selecting the antigen one desires to identify and isolating specific antibody or antibodies which are labeled with detectable labels, which includes fluorescent labels (column 5, lines 40-65). Georgiou teaches that the preferred are host cells from gram-negative bacteria such as *E. coli* (column 7, lines 50-53). Georgiou teaches that *E. coli* cultures were grown at 24°C or 37°C (column 22, lines 61-64). Georgiou teaches that identifying the antibody or antibody fragment expressing cells may be accomplished by methods that depend on detecting the presence of the bound detectable label. Georgiou teaches that a preferred identification and isolation is cell sorting or flow cytometry and that one aspect of this method is fluorescence activated cell sorting (FACS) (column 6, lines 4-9). Georgiou teaches that the analyte (candidate binding protein) of particular interest are amino acids, peptides, proteins, lipids, saccharides, nucleic acids and combinations thereof (column 6, lines 32-50). Georgiou teaches that a particular advantage of cell surface (periplasm) expressed antigen-binding antibodies is that the antibody is attached to the outer membrane of the cell (column 6, lines 63-65) and that the surface displayed antibodies or antibody conjugates may be catalytic antibodies or antibody conjugates such as fusion protein that include reporter molecules, e.g. alkaline phosphatase, luciferase and β-lactamase (column 8, lines 54-63). Georgiou teaches that the cells with the antibody displayed on the surface may themselves be attached to a solid support such as a membrane, dipstick or beads to further facilitate removal of the cells (column 7. lines 2-5). Georgiou et al teach that detectable labels that may be used in the invention are radioactive, fluorescent, chemiluminescent and

electrochemiluminescent agents (column 8, lines 35-42). Georgiou et al teach that cells were harvested and resuspended in PBS pH 7.4 at a concentration of 10^{10} cell/ml based on the $O.D._{600}$ to form a cell shock and some cells were resuspended in 15 % glycerol /water and stored at 70°C (i.e. hyperosmotic conditions and physical stress) (column 39, lines 40-47). Limitations such as the ligand comprise a molecular weight of less than about 20,000 Da, less than about 5,000 Da and a molecular weight greater than 600 Da and less than about 30,000 Da would be inherent in the teachings of the prior art.

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Iverson et al (*WO 98/49286, published November 5, 1998)* or Georgiou *(U.S. Patent No. 5,866, 344, published February 2, 1999)* in view of Pini et al *(The Journal of Biological Chemistry,1998, Vol. 273, No. 34, p. 21769-21776).*

Claim 26 is drawn to the method of claim 24 comprising treating the bacterium with a phage.

Iverson teach a method of screening of antibody libraries displayed on the cell surface. Iverson et al teach that the "expression construct" is a genetic construct containing a nucleic acid coding for a gene product in which part or all of the nucleic acid is capable of being transcribed. Iverson et al teach the amplification of gene fragments (pages 39-43). Iverson et al teach that the host cell is a gram-negative bacterium, *E. coli* (claims 2-3, page 123) and that a plurality of DNA segments are incorporated into expression vectors and the vectors express antibodies or antibody fragments on the outer membrane surface (the periplasm) of *E. c*oli (claim 11, page 124).

Georgiou teaches a method of obtaining a bacterium comprising a nucleic acid sequence encoding a binding protein capable of a target ligand comprising the steps of: Obtaining antibodies from an expression vector library that may be prepared from DNAs encoding antibodies or antibody fragments, selecting the antigen for one desires to identify and isolating specific antibody or antibodies which are labeled with detectable labels, which includes fluorescent labels (column 5, lines 40-65). Georgiou teaches that *E. coli* cultures were grown at 24°C or 37°C (column 22, lines 61-64). Georgiou

teaches that identifying the antibody or antibody fragment expressing cells may be accomplished by methods that depend on detecting the presence of the bound detectable label. Georgiou teaches that a preferred identification and isolation is cell sorting or flow cytometry and that one aspect of this method is fluorescence activated cell sorting (FACS) (column 6, lines 4-9). Georgiou teaches that a particular advantage of cell surface (periplasm) expressed antigen-binding antibodies is that the antibody is attached to the outer membrane of the cell (column 6, lines 63-65)

Iverson et al or Georgiou do not teach the use of phages.

Pini et al teach the use of phages in constructing antibody libraries (see the Abstract). Pini et al teach that phage antibody display technology is simple, inexpensive and lends itself to simultaneous processing of several antigens (page 21769, 2nd column) and that synthetic antibody repertoires constructed with a single germ line segment have reliably yielded good binders against a large variety of antigens (page 21774, 1st column).

It would be *prime facie* obvious at the time the invention was made to treat the bacterium used in the methods of screening antibody libraries as taught by Iverson et al or Georgiou et al with phages as taught by Pini et al because Pini et al teach that phage antibody display technology is simple, inexpensive and lends itself to simultaneous processing of several antigens (page 21769, 2nd column) and that synthetic antibody repertoires constructed with a single germ line segment have reliably yielded good binders against a large variety of antigens (page 21774, 1st column). It would be expected barring evidence to the contrary that the use of phage antibody technology

can be used to produce large functional antibody libraries and because several biological applications high-affinity binders are needed, the phage library may be constructed in a way that allows the ~~facile~~ facility of affinity maturation of antibodies of interest (page 21769, 2nd column).

Status of Claims

11. No claims are allowed.

Pertinent Art

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure *(Georgiou et al, U.S. Patent Number, 5,48,867, published September 20, 1994, Ladner et al, U.S. patent Number, 5,223,409, published June 29, 1993 and Daugherty et al, Protein Engineering, Vol. 12, No. 7, p. 613-621).*

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Conclusion

13. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
April 4, 2002